

A I D S TREATMENT N E W S

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AIDS Treatment News

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Statement of Purpose:

AIDS Treatment News reports on experimental and standard treatments, especially those available now. We interview physicians, scientists, other health professionals, and persons with AIDS or HIV; we also collect information from meetings and conferences, medical journals, and computer databases. Long-term survivors have usually tried many different treatments, and found combinations that work for them. *AIDS Treatment News* does not recommend particular therapies, but seeks to increase the options available.

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Medicine has not made full use of online information -- and doing so might save thousands of lives. Part I looks at what has been most successful online in other fields, for background on how medical information could be improved.

Brain Drain Adds To AIDS Crisis in Developing World.....

Thousands of desperately needed doctors and other medical professionals leave poor countries because no one there can pay them, or provide safe and effective working conditions. Many go to English-speaking countries that do not train enough medical professionals themselves -- such as the U.S., where a quarter of the doctors are foreign trained.

Brazil: Gilead Cuts Tenofovir Price in Half.....

A U.S. activist campaign, centered in the San Francisco area near Gilead's headquarters, helped get this major price reduction for Brazil's model HIV treatment program.

AIDS Treatment News Returns.....

After five months we are publishing again.

Prezista (Darunavir, TMC-114) Approved; May Be Important Treatment Advance

by John S. James

Prezista (also called darunavir, or TMC-114), a new protease inhibitor active against many of the viruses resistant to other protease inhibitors, was approved by the FDA on June 23 "for the treatment of human immunodeficiency virus (HIV) infection in antiretroviral treatment-experienced adult patients, such as those with HIV-1 strains resistant to more than one protease inhibitor." In hard-to-treat patients already highly resistant to other antiretrovirals, 70% of patients taking Prezista together with other HIV treatments had a virologic response at week 24, vs. 21% of patients on other treatments only, according to the FDA's analysis.

Prezista must be taken with a small dose of ritonavir, and also with food (the type of food is not important). Otherwise, the level of

Prezista in the blood will be too low, greatly increasing the risk of viral resistance. Prezista is supplied as 300 mg tablets; the usual adult dose is two of these tablets plus 100 mg of ritonavir, taken twice a day with food (a total of 4 Prezista tablets and two 100-mg ritonavir tablets per day).

While Prezista was designed to overcome viral resistance to other protease inhibitors, resistance to the drug itself can develop. Some of the patients in the trials already had cross resistance to Prezista when the trial began (due to their extensive resistance to other protease inhibitors), and it got worse on the average, as they used the drug -- showing the importance of having more than one active antiretroviral, instead of introducing new drugs one by one as they become available, and then often losing them to resistance.

Price and Access -- An Activist Victory

Tibotec, a Belgian company that specializes in designing new drug molecules engineered to prevent resistance, developed Prezista. Tibotec did not have the money to complete the very expensive large clinical trials, so it was acquired by Johnson & Johnson, which provided the money and was able to get the trials moving rapidly, resulting in the current approval.

Shortly after approval, the price was set at \$25 a day (wholesale acquisition price) -- at the low end of the last three protease inhibitors approved (the ritonavir will cost extra). This was a clear change from the recent past, where each new drug set a new price record. Companies have called the routine escalation "value benchmark" pricing, saying that the new drug was more valuable so it justified a higher price. Without the activism noted below, the price could have been more than twice as high -- preventing the drug from ever being widely used for first-line treatment, where the need is not immediate and desperate, since other good treatments are available for these patients.

In fact, each antiretroviral has complex advantages and disadvantages; most new ones are more equivalent than superior to existing treatments, except for a small fraction of patients who strongly benefit -- the advantage of having more choice instead of less. And

cumulatively, the steady price escalation has caused drugs to be used irrationally because patients and public programs cannot afford reliable supplies, leading to unplanned interruptions and people not receiving the medication they need.

High prices also increase incentives for private insurance and public programs to use various means of restricting access, depriving doctors and patients of choice, especially when they want to use a treatment off-label (prescribe an approved drug for a use not specifically approved by the FDA) -- universally recognized as an important part of medicine since companies cannot possibly run clinical trials for all appropriate uses, and therefore the FDA cannot approve them. But for private and public insurance, off-label status provides an excuse not to pay for more expensive treatment. Private insurance has no financial incentive to keep expensive patients alive; in fact, the incentives are the opposite, especially since the federal government has largely ruled out lawsuits in such cases. Obviously we need healthcare reform to deal with price, insurance, and other abuses, but that has not happened so far due to current politics. U.S. institutions are run for the short-term benefit of major corporations and elite insiders, not for the long-term viability of the society or for the benefit of the great majority of its people.

Before the approval of Prezista and long before the price was announced, activists loosely organized as the Fair Pricing Coalition began a campaign to talk to the leadership of Tibotec Therapeutics about the "growing national and international crisis in the cost of health care" and the need for corporate responsibility. Hundreds of community organizations and individuals signed a consensus letter to Tibotec for pricing that is cost neutral, instead of pushing up the cost of treatment with every new drug. Tibotec responded, and broke the unsustainable cycle of big price increases every time.

The lower price could well be in the company's financial interest, by allowing first-line use if the drug proves suitable -- especially important now that its rival Aptivus (tipranavir) does not seem to be working well as a first-line treatment, with a clinical trial stopped because of performance that appeared slightly inferior to a good standard treatment based on Kaletra. [1] We have not seen an analysis of that trial, but the general picture is that while a very good resistance profile (such as with Aptivus, or Prezista) is of course a benefit in first-line

use because it is likely to extend the success of the regimen, the overall performance of a drug depends on many factors, including tolerability of side effects so that patients can continue taking it. First-line use (by patients who have never taken antiretrovirals) must compete against fairly good standard treatment options. Since Prezista was fortunately tested first for those who needed it most, we do not have such comparisons yet.

For More Information

One place to start is the *PREZISTA (darunavir) Tablets - Patient Information* sheet, which should be included with each bottle of the tablets. It can also be found on the Web, probably at <http://www.prezista.com/> (the site was not ready when this issue went to press).

For much more detail see the prescribing information for physicians, which should also be on that site. Incidentally, the information for patients is also included as the last six or so pages of the document for physicians.

For information on the pricing campaign, see "Activists Say New HIV Drug Price Encouraging," by Tim Horn, <http://www.aidsmeds.com/news/am20060627.html>

Also see the lead article in the latest issue of *Project Inform Perspective*, (published before the price was set), <http://www.projectinform.org/pip/41/pip41.html> (Do *not* write to Tibotec as directed; that campaign is over as the company has already announced a price much lower than what was feared. The excellent consensus statement to Tibotec, and lists of signers, is at <http://www.champnetwork.org/index.php?name=tibotec-letter>

References

1. "Tipranavir [Aptivus] Study Halted in Treatment-Naive," by Keith Alcorn, Aidsmap, June 21, 2006, <http://www.aidsmap.org/en/news/1F626F94-0A95-485B-84F3-D4C095B73CB2.asp> (It may be easier to go to <http://www.aidsmap.org> and type the first three words of the title into the search box at the upper right of the page).

Study Finds 3,000,000 Years of Life Saved by

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HIV Treatment in the U.S.

A detailed study of the population-wide benefit of AIDS treatment improvements (both antiretrovirals and other treatment) estimated that at least 3,000,000 years of life have been saved in the U.S. so far, compared to no treatment. The paper and an accompanying editorial were published in the *Journal of Infectious Diseases*, and they are available free online.

For More Information

The full article, including a link to the accompanying editorial, is at <http://www.journals.uchicago.edu/JID/journal/issues/v194n1/35845/35845.html>

You can also find reporting about this article by doing the following Google search: HIV "three million"

Vaccine Improves Survival in Monkey Tests

by John S. James

Researchers at the U.S. National Institute of Allergy and Infectious Diseases (NIAID) reported that an experimental vaccine clearly improved the survival of monkeys after infection by SIV (simian immunodeficiency virus), a virus similar to HIV -- even though it did not prevent infection, and did not much improve viral load or total T-cell count.

While the viral load and T-cell count did not predict the greater survival, something else did -- measurement of memory cells (one kind of T-cells) in the first few months of infection. Memory cells make up more than half of T-cells in adults, and early in HIV disease many of these cells are infected and eventually lost. In the monkey test, three to five times fewer of the memory cells were infected in vaccinated animals than in unvaccinated animals.

The vaccine used in this study was a simplified version of an HIV vaccine now in phase II human trials in the U.S. and some other countries.

Besides the possibility of a survival benefit in humans even if a vaccine fails to prevent infection, this is important for additional reasons:

- The researchers found an immune response from a vaccine that did help protect the animals. A big problem in HIV vaccine research has been that while it is easy to show

immune responses to HIV vaccines, it has been very hard to find "correlates of protection" -- that is, responses that do any good at protecting against HIV-type viruses.

- If this result is confirmed in humans, it could give a much earlier indication of which vaccines are promising and which are not. This early information could help with another big problem in vaccine research. Since no one would deliberately infect people with HIV in order to test a vaccine, trials have to study thousands of people for years to prove that a vaccine works. Very few such studies can be done, so it is critically important to get the best candidate vaccines into these large phase III trials. An early indicator that can be measured in every patient, and is known to predict survival, would help immensely.

- The fact that the monkeys benefited even partly creates a framework for studying HIV pathogenesis (development of the disease) -- and studying how vaccines might work, as well as immune-based or other new kinds of treatment for those already infected. Without the observed benefit to the animals, lots of data could still be collected, but it might be difficult or impossible to know which findings were meaningful and which were not.

For More Information

NIAID published a press release, "Monkeys Vaccinated Against SIV Survive Longer After Infection" on June 9. You can find it at <http://www3.niaid.nih.gov/news/newsreleases/2006/SIVvax.htm>

This press release includes references to the two articles, one in *Science*, and the other in *Journal of Experimental Medicine*.

XVI International AIDS Conference, Toronto, August 13-18, 2006; Record Number of Abstracts: India, Nigeria, South Africa, Brazil, Uganda Strongly Represented

The International AIDS Conference takes place every two years, and the 16th meeting will be in Toronto, Canada, August 13-18. A record 12,888 abstracts were submitted for blind peer review, and 9,826 are being published: 365 oral presentations, 200 poster-discussion presentations, 3,843 poster presentations, and 5,418 on the CD-ROM given to all participants. All will be published online. ^{line}

Of the accepted abstracts, the top 21 countries with the number of abstracts accepted and scheduled to be presented were: United States 1819; India 723; Canada 606; Nigeria 594; South Africa 439; Brazil 405; Uganda 368; United Kingdom 316; Kenya 267; Thailand 259; China 218; France 171; Mexico 139; Zambia 136; Nepal 132; Cambodia 129; Tanzania 129; Russian Federation 112; Australia 105; Bangladesh 101; and Malawi 101. All abstract submission, even for "late breakers," is now closed.

Skills-building presentations were separately peer reviewed, and 86 were accepted of 766 submitted. A two million dollar scholarship program will allow 815 applicants to attend -- the great majority from resource-limited countries. Another program awarded 1,100 scholarships to Canadian residents.

For more information see <http://www.aids2006.org/>

AIDS History Research: New ArchiveGrid Available

People researching the history of AIDS (or AIDS activism, particular organizations like ACT UP, or individual public figures) may get invaluable help from private collections of papers that have been donated to university libraries and other institutions. The problem has been finding out what collections exist and where they are located. Now a new service for scholars called ArchiveGrid is getting rave reviews; it was free through June 2006, and currently offers both institutional and individual accounts.

For example, go to <http://www.archivegrid.org> and use the search box near the upper left of the screen to search for "ACT UP" (with the quotation marks). In June 2006, 61 collections were found. ArchiveGrid has a short description of each, contact information for the appropriate department at the library, and sometimes a link to a library page with more information about the collection. Each library has its own rules for access (including restrictions from the original donors, who may have confidentiality concerns).

A search on "HIV" (quotation marks not needed) found a total of 201 collections and other items. Probably all of them are relevant to AIDS. Searching for "Philadelphia HIV"

without the quotation marks found 32 that mention both. ("Philadelphia" alone found over 73,000 historical collections, etc. that mention the city.)

The great majority of collections indexed are in the United States at this time, but a few are in Australia or UK. Over 3,000 libraries and other organizations have contributed information to ArchiveGrid (see list on site).

ArchiveGrid tried to raise funds to maintain free access, but currently (July 2006) it must charge \$15.95 per month or \$95 per year for individual use. This is affordable even for unfunded research projects, because usually one month of access will be enough to locate relevant collections of materials, and the ArchiveGrid database changes very slowly. Also, without paying anything you can run your searches to find the total number of hits, and titles only of the first three items, to learn whether the service will be relevant for your project.

Fundraising Note

This writer designed software for gift-economy distribution of any digital information, including art, medical journals, or services like ArchiveGrid. Anyone could buy any amount of access and receive it in a smart URL (Web link), then easily share their access through social networks as they wished. Most downloads will be free, simply a click with no registration or account required -- and the act of free downloading itself will instantly pay the artist, publisher, or other owner. For more information, wait for our article on medical uses, or see our general site at <http://www.smart-accounts.org>.

Improving Medical Communication Online

by John S. James

In the past few years some Web sites have become enormously successful, providing services useful enough to attract many millions of visitors, even without advertising. (When was the last time you saw an ad for Google?) This communication revolution builds largely on information contributed by multitudes of users -- not just by a few celebrities or by management. Information is the lifeblood of science and medicine; a similar revolution in

medical communication could be worth billions of dollar a year by making all of medical research and medical practice more effective -- while saving thousands of lives, and improving the everyday health of millions.

Medicine has its own needs and must find its own way, not simply follow what works elsewhere. A key difference is that medicine and science rate information based on the authority of expert peer review, while many successful Web sites use other forms of popularity for their ratings.

But imagine a world where individuals could choose among many different flavors and philosophies of expert review, and mix or change these "views" of the universe of available information at any time. Also, informal recommendations by many different experts, public figures, organizations, and others could help everyone manage information overload, by combining expert and popular referrals to help people find what they most want or need, and what others in their situation have found most helpful.

These reviews and recommendations could help individuals navigate an AIDS conference -- or recent scientific or medical publications -- or the entire body of information published on the Web as it relates to a particular medical need. Important work even by unknown authors could be widely recognized immediately, if it is accurate and uniquely useful.

Our next issue will propose such designs for medicine. Here we look at sites that already work very well online in other fields, to see what can be learned from them.

Successful Internet Models

Some online communication system to look at (but not necessarily copy for medical use) include:

- **Wikipedia** (<http://www.wikipedia.org>), the free online encyclopedia written by volunteers, has much more information than *Encyclopedia Britannica* and is almost as accurate, according to a recent study by the leading science journal *Nature*. [1] Wikipedia now has over 4,000,000 articles in 200 language editions -- about 1.2 million in English. No one thought that an encyclopedia could be written that way -- not even those who started this one, as an afterthought to another project. Wikipedia is now the 11th most popular Web site in the U.S. and the 16th most popular in the world (2006-06-21), according to

Alexa traffic rankings. [2]

The Wikipedia concept might also be applied to free or low-cost online textbooks as well, to greatly improve medical and other education around the world. Student would not have to pay hundreds of dollars a year for books, developing countries would have access to the world's best, and teachers could create custom views or edited selections tailored for their classes, and share these with colleagues around the world. Copyright restrictions would largely go away, and students could study anywhere from print, iPods or other portable media, or their computer screen. Companies getting rich on overpriced textbooks could find something else to do.

A June 17 article in *The New York Times* describes how Wikipedia deals with the disputes, fights, and vandalism that occur from letting anyone online in the world write or change entries in so influential a publication. [3] What most surprised us is that Wikipedia had to restrict fewer than 300 articles out of the 1.2 million in English -- and most of these had only the mild restriction of limiting editing to users who had registered at least four days prior, and even that is often temporary. While anyone can write or change most entries, in practice Wikipedia is mostly written by a community of about 1,000 volunteer writers and editors around the world, who have often nominated each other and generally built relationships of trust over time. This community has also developed software tools that help it promptly detect and control abuse.

- **Craigslist** (<http://www.craigslist.com>), like Wikipedia a non-commercial site, has become the world's biggest classified advertising system in any medium. (Alexa ranks Craigslist as 7th most popular in the U.S.)

- **YouTube** (<http://www.youtube.com>), which lets people put their own videos online to share with anyone, became one of the most visited sites on the Internet within one year. It followed the success of Flickr (<http://www.flickr.com>), which similarly let people publish their photographs. (Alexa rates YouTube as 19th most visited in the U.S.)

- **MySpace** (<http://www.myspace.com>), an Internet site widely used by young adults, has over 80 million user accounts, and is the third most visited U.S. site according to Alexa. Probably a fraction of users (but still millions of people) account for most traffic. How did this site become so popular?

MySpace was started by software experts to provide their friends with the computer facilities they wanted. All in one place people can set up their own user profiles, Web sites, blogs, social networking, forums, and good ways to share their own work in music, videos, photos, and other media. While the pioneering social-networking site Friendster marginalized itself by fighting its users, MySpace cooperated and gave them most of what they wanted (with important exceptions, such as forbidding links to other Web sites, or the very limited opportunities to earn income on MySpace).

In July 2005 MySpace was purchased for \$580 million by Rupert Murdoch -- the media tycoon famous for using his journalistic properties as shills for war in Iraq [4], supposedly to give the world \$20 oil (it is now over \$70), but more likely in trade for U.S. government favoritism toward his empire.

The MySpace "Terms & Conditions" (May 1, 2006 version) prohibit "any telephone numbers, street addresses, last names, URLs or email addresses" being posted or transmitted on the service -- making users more vulnerable to excommunication by making it harder for them to integrate their MySpace world ("a place for friends") with the rest of their lives. In late March 2006, MySpace said that it had removed 200,000 user profiles that it considered objectionable (for either hate or love, according to news reports -- "hate speech" or "too risqué" -- though probably no one outside the company has a good picture of what happened).

Two hundred thousand people may not seem like many for a site gaining 250,000 new users per day. But it gives the company influence over millions, by establishing a threat of disconnection from part of their lives. And MySpace gains more influence by publicizing whatever user activities it wants on high-traffic pages -- highly valued rewards on a site that is all about attention. Users who want to succeed there will naturally assume that they should not cross Murdoch or the corporate establishment he represents, either on MySpace or anywhere else.

The shadow over the future is ominous. If it becomes smart and sophisticated to accept abuses such as massive promotion of a war for personal business interests, what kind of world will we leave to future generations?

The fundamental problem is private ownership of human communities -- digital company towns where the owner has absolute

power, and the entire history of due process and personal rights in human society does not apply. How much of their lives will people put into such things? That depends on the alternatives available. In later articles we will look at strategies for reducing dependency on the new company towns, whether or not one chooses to use them.

- **Google (<http://www.google.com>)** has become one of the largest and most profitable media companies in the world, mainly on the strength of its central innovation, a rating system that shows people the most linked-to Web pages first (popularity among writers of other Web sites, weighted according to the importance of those sites). And Google had the insight to realize that a search string enabled the targeting of advertisements, greatly increasing their value to the public and therefore to the advertiser.

Yet Google remains vulnerable despite its great wealth, because searchers could leave in a moment if anything more useful came along. For example, Ask.com (<http://www.ask.com>) uses link popularity among expert sites, instead of link popularity in general as Google does; a search for "HIV" returns a more useful top 30 sites (not counting the advertising at the top and bottom) compared to a Google search. And on May 1, 2006, Amazon.com (including Alexa) announced that it dropped Google's search for Microsoft's.

Google could end one vulnerability by fixing its handling of dates -- so you could see the top 100 or whatever sites in order with the most recent significant updates first, instead of seeing the last five years or so mixed arbitrarily together. The right way to do this is also the easy way -- fix the whole Web. Google has the influence to standardize dates throughout the Web, by announcing that it would give search priority to pages that had an honest date in the international date format, yyyy-mm-dd [5] -- at least when users asked to see sites by date. The sites that account for the great majority of search results care greatly about their Google search position, and would quickly standardize their dates if necessary to gain this advantage. (Google's Advanced Search has a simple date test, but it does not work well; for example, a search for "Pennsylvania" found 9,000,000 more pages dated in the last six months than dated any time, as of 2006-06-29 -- the date-range numbers change frequently.)

In Alexa, Google ranks as the second most

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popular Web site among U.S. visitors, after Yahoo, (not surprising since Yahoo has traditionally offered a wider range of services, while most people only use Google for search).

Note that all these very successful sites are free, and all of them give users lots of valuable information and a good experience without making them register first. (Usually visitors do need to register or sign up in some way before publishing their own comments or other information on these sites, but typically such sign-up is minimal: make up a user name and password, provide an email address that must work, read a few funny-looking numbers or letters to prove you are a person not a robot, agree to the terms and conditions, and confirm as instructed by email. Or just be signed up already at a cooperating site.)

For more information about these and other online communication systems that have been most successful recently on the Web, see the special section "Among the Audience" in *The Economist*, April 20, 2006. [6]

Part II of this article will look at major problems in medical communication today, and explore possible improvements.

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1. Giles, J. Internet encyclopedias go head to head. *Nature*. December 15, 2005; volume 483, pages 900-901, <http://dx.doi.org/10.1038/438900a> For a BBC news report, see <http://news.bbc.co.uk/2/hi/technology/4530930.stm>

2. Alexa, owned by Amazon.com, lists traffic rankings for the top 100 sites in each of over 70 countries; it gets the information by offering people a toolbar that provides additional search help, in return for automatically reporting users' Web use to Alexa. Visit http://www.alexa.com/site/ds/top_500 and click "United States" or another country, or click "See more Global Top 500."

You can get the Alexa traffic ranking for almost any Web site -- and see the top sites its visitors also visit. At <http://www.alexa.com> click the "Traffic Rankings" tab. Type the site you want to check into the box, and click "Get Traffic Details."

These rankings are not perfect, due to self-selection, operating-system, and other biases in who uses the toolbar that reports the Web sites they visit. But the information is free, easy to use, available to everybody and good enough for many discussions.

3. "Growing Wikipedia revises Its 'Anyone can edit' policy," *The New York Times*, 2006-06-17.

4. "Their Master's Voice," *The Guardian* (UK), 2003-02-17